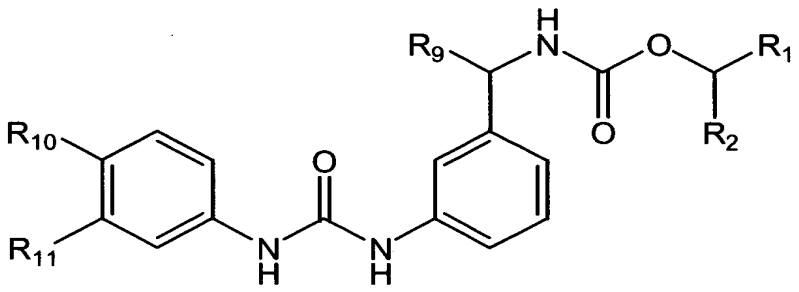
CLAIMS

We claim:

1. A composition comprising:

(a) an apoptosis inducing anti-cancer agent;

(b) a compound of formula (A):



(A)

wherein:

each of R_1 and R_2 is independently selected from hydrogen; $-CF_3$; $-(C_1-C_6)$-straight or branched alkyl; $-(C_2-C_6)$-straight or branched alkenyl or alkynyl; $-(C_1-C_6)$-straight or branched alkyl-R_7; $-[(C_2-C_6)$-straight or branched alkenyl or alkynyl$]-R_7$ or $-R_7$; and wherein at least one of R_1 or R_2 is $-(C_1-C_6)$-straight or branched alkyl-R_7; $-[(C_2-C_6)$-straight or branched alkenyl or alkynyl$]-R_7$ or $-R_7$

wherein up to 4 hydrogen atoms in any of said alkyl, alkenyl or alkynyl are optionally and independently replaced by R_3; and

wherein one or both of R_1 or R_2 are optionally esterified to form a prodrug; or

wherein R_1 and R_2 are alternatively taken together to form tetrahydrofuranyl, wherein when R_9 is hydrogen, (R)-methyl, (R)-ethyl or (R)-hydroxymethyl, one hydrogen atom in said tetrahydrofuran is replaced by $-OR_6$

or $-R_7$, and wherein when R_9 is (S)-methyl, (S)-ethyl or (S)-hydroxymethyl, one hydrogen atom in said tetrahydrofuran is optionally replaced by $-OR_6$ or $-R_7$;

wherein when R_9 is hydrogen, (R)-methyl, (R)-ethyl or (R)-hydroxymethyl and each of R_1 and R_2 are independently hydrogen, unsubstituted $-(C_1-C_6)$-straight or branched alkyl, or unsubstituted $-(C_2-C_6)$-straight or branched alkenyl or alkynyl, then the portion of the compound represented by $-CH(R_1)R_2$ is a C_5-C_{12} straight or branched alkyl, alkenyl or alkynyl;

each R_3 is independently selected from halo, CN, $-OR_4$, or $-N(R_5)_2$;

R_4 is selected from hydrogen, $-(C_1-C_6)$-straight or branched alkyl, $-(C_2-C_6)$-straight or branched alkenyl or alkynyl, $-[(C_1-C_6)$-straight or branched alkyl$]-R_7$, $-[(C_2-C_6)$-straight or branched alkenyl or alkynyl$]-R_7$, $-C(O)-[(C_1-C_6)$-straight or branched alkyl], $-C(O)-[(C_2-C_6)$-straight or branched alkenyl or alkynyl], $-C(O)-[(C_1-C_6)$-straight or branched alkyl$]-N(R_8)_2$, $-C(O)-[(C_2-C_6)$-straight or branched alkenyl or alkynyl$]-N(R_8)_2$, $-P(O)(OR_8)_2$, $-P(O)(OR_8)(R_8)$, $-C(O)-R_7$, $-S(O)_2N(R_5)_2$, $-[(C_1-C_6)$-straight or branched alkyl$]-CN$, or $-[(C_2-C_6)$-straight or branched alkenyl or alkynyl$]-CN$;

each R_5 is independently selected from hydrogen, $-(C_1-C_6)$-straight or branched alkyl, $-(C_2-C_6)$-straight or branched alkenyl or alkynyl, $-[(C_1-C_6)$-straight or branched alkyl$]-R_7$, $-[(C_2-C_6)$-straight or branched alkenyl or alkynyl$]-R_7$, $-[(C_1-C_6)$-straight alkyl$]-CN$, $-[(C_2-C_6)$-straight or branched alkenyl or alkynyl$]-CN$, $-[(C_1-C_6)$-straight or branched alkyl$]-OR_4$, $-[(C_2-C_6)$-straight or branched alkenyl or alkynyl$]-OR_4$, $-C(O)-(C_1-C_6)$-straight or branched alkyl, $-C(O)-[(C_2-C_6)$-straight or branched

alkenyl or alkynyl], $-C(O)-R_7$, $-C(O)O-R_7$, $-C(O)O-(C_1-C_6)$-straight or branched alkyl, $-C(O)O-[(C_2-C_6)$-straight or branched alkenyl or alkynyl], $-S(O)_2-(C_1-C_6)$-straight or branched alkyl, or $-S(O)_2-R_7$; or two R_5 moieties, when bound to the same nitrogen atom, are taken together with said nitrogen atom to form a 3 to 7-membered heterocyclic ring, wherein said heterocyclic ring optionally contains 1 to 3 additional heteroatoms independently selected from N, O, S, S(O) or $S(O)_2$;

R_6 is selected from $-C(O)-CH_3$, $-CH_2-C(O)-OH$, $-CH_2-C(O)-O-tBu$, $-CH_2-CN$, or $-CH_2-C\equiv CH$;

each R_7 is a monocyclic or bicyclic ring system wherein in said ring system:

i. each ring comprises 3 to 7 ring atoms independently selected from C, N, O or S;

ii. no more than 4 ring atoms are selected from N, O or S;

iii. any CH_2 is optionally replaced with C(O);

iv. any S is optionally replaced with S(O) or $S(O)_2$;

each R_8 is independently selected from hydrogen or $-[C_1-C_4]$-straight or branched alkyl;

wherein in any ring system in said compound up to 3 hydrogen atoms bound to the ring atoms are optionally and independently replaced with halo, hydroxy, nitro, cyano, amino, (C_1-C_4)-straight or branched alkyl; $O-(C_1-C_4)$-straight or branched alkyl, (C_2-C_4)-straight or branched alkenyl or alkynyl, or $O-(C_2-C_4)$-straight or branched alkenyl or alkynyl; and

wherein any ring system is optionally benzofused;

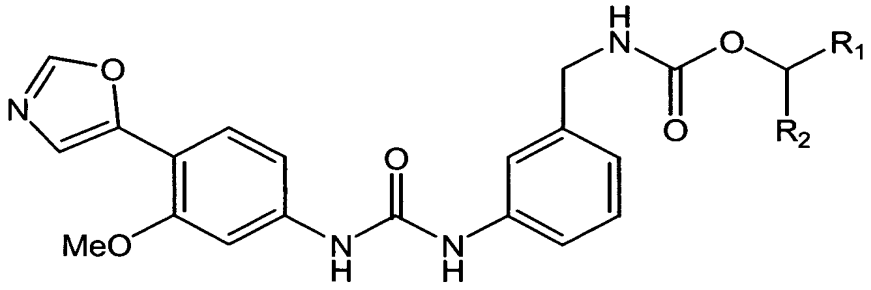
R_9 is selected from hydrogen, (R)-methyl, (S)-methyl, (R)-ethyl, (S)-ethyl, (R)-hydroxymethyl or (S)-hydroxymethyl;

R_{10} is selected from -C=N or 5-oxazolyl; and

R_{11} is selected from halo, -O-(C_1-C_3) straight alkyl, or -O-(C_2-C_3) straight alkenyl or alkynyl;

(c) a pharmaceutically acceptable carrier.

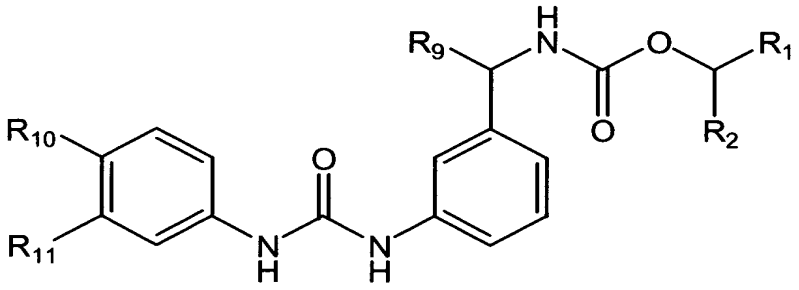
2. The composition according to claim 1, wherein said compound has the formula (I):



(I) ;

wherein R_1 and R_2 are as defined in claim 1.

3. The composition according to claim 1, wherein said compound has the formula (IA):



(IA);

wherein R_9 is selected from (R)-methyl, (S)-methyl, (R)-ethyl, (S)-ethyl, (R)-hydroxymethyl or (S)-hydroxymethyl; and

R_1 and R_2 are as defined in claim 1.

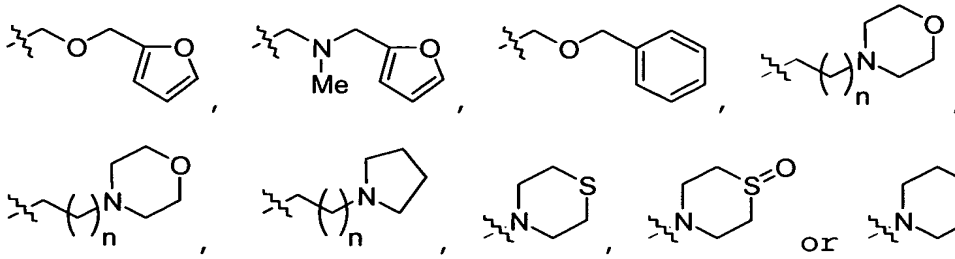
4. The composition according to claim 3, wherein R_9 is selected from (S)-methyl, (S)-ethyl, or (S)-hydroxymethyl methyl.

5. The composition according to claim 4, wherein R_9 is (S)-methyl.

6. The composition according to claim 3, wherein R_{11} is selected from O-methyl, O-ethyl or O-isopropyl.

7. The composition according to claim 1, wherein:

at least one of R_1 or R_2 is selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, phenyl, pyridyl, $-CH_2OCH_3$, $-CH_2CN$, $-CH_2OCH_2CH_2CN$, $-CH_2C(CH_3)_2CH_2CH_2CN$, $-CH_2C(CH_2CH_3)_2CH_2CH_2CN$, $-CH_2CH_2CN$, $-CH_2N(CH_2CH_2CN)_2$, $-CH_2N(CH_3)CH_2CH_2CN$, $-CH(NH_2)CH_2CN$, $-CH_2Cl$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2CH_2OH$, $-CH_2CH_2OC(O)CH_3$, $-CH_2CH_2OC(O)CH_2NH_2$, $-CH_2CH_2NHCH_3$, $-CH_2CH_2N(CH_3)_2$, $-CH_2N(CH_2CH_3)_2$, $-CH_2CH_2N(CH_2CH_3)_2$, $-CH_2CH_2CH_2N(CH_3)_2$, $-CH_2CH_2CH_2N^+(CH_3)_3$, $-CH_2OCH_2CH(CH_3)_2$, $-CH_2CH_2N(CH_3)C(O)OC(CH_3)_3$, $-CH_2N(CH_2CH_2CN)CH_2CH(CH_3)_2$, $-CH(CH_2CN)N(CH_3)_2$, $-CH_2CH(CH_2CN)NHC(O)OC(CH_3)_3$,



wherein n is 0 or 1.

8. The composition according to claim 2,

wherein R_1 and R_2 are taken together to form a 3-tetrahydrofuranyl moiety that is substituted at the 5 position by $-OR_6$.

9. The composition according to claim 3, wherein one of R_1 or R_2 is selected from hydrogen, ethyl or phenyl; and the other of R_1 or R_2 is selected from $-CH_2OH$, $-CH_2CN$, $-CH_2CH_2CN$ or $CH_2N(CH_2CH_3)_2$; or wherein R_1 and R_2 are taken together to form a 3-tetrahydrofuranyl moiety.

10. The composition according to claim 1, wherein said compound is selected from any one of compounds 1 to 187 in Table 1.

11. The composition according to claim 10, wherein said compound is selected from any one of compounds 1, 23, 26, 27, 29, 32, 76, 80, 87, 89, 98, 101, 103, 104, 106, 108, 110, 157, 163, 169, 171, 181, 185, 186 or 187 in Table 1.

12. The composition according to any one of claims 1-11, wherein said apoptosis inducing anti-cancer agent is an anti-metabolite.

13. The composition according to claim 12, wherein said anti-metabolite is selected from cytarabine, fludarabine, 5-fluro-2'-deoxyuridine, gemcitabine, hydroxyurea, or methotrexate.

14. The composition according to claim 13,

wherein said anti-metabolite is selected from cytarabine, fludarabine, or 5-fluro-2'-deoxyuridine.

15. The composition according to claim 14, wherein said anti-metabolite is selected from fludarabine or cytarabine.

16. The composition according to claim 15, wherein said anti-metabolite is fludarabine.

17. The composition according to claim 13, wherein said anti-metabolite is hydroxyurea or methotrexate.

18. The composition according to claim 17, wherein said anti-metabolite is methotrexate.

19. The composition according to any one of claim 12-18, wherein said compound is selected from compound No. 169 and 181.

20. A method for inhibiting tumors and cancer in a mammal comprising the step of administrating to said mammal a composition according to any one of claims 1-19.

21. The method according to claim 20, wherein said method is useful to treat or prevent lymphoma, leukemia and related disorders, myelodysplastic syndrome, metastatic melanoma, and other forms of cancer.